

QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability

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Batchvarov, Velislav N., Azad Ghuran, Peter Smetana, Katerina Hnatkova, Monica Harries, Polychronis Dilaveris, A. John Camm, and Marek Malik. QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. *Am J Physiol Heart Circ Physiol* 282: H2356–H2363, 2002. First published February 21, 2002; 10.1152/ajpheart.00860.2001.—Recently, it was demonstrated that the QT-RR relationship pattern varies significantly among healthy individuals. We compared the intra- and interindividual variations of the QT-RR relationship. Twenty-four-hour 12-lead digital electrocardiograms (ECGs; SEER MC, GE Marquette; 10-s ECG recorded every 30 s) were obtained at baseline and after 24 h, 1 wk, and 1 mo in 75 healthy subjects (42 women, 33 men, age 27.9 ± 9.6 vs. 26.8 ± 7.5 yr, $P =$ not significant). QT interval was measured automatically in each ECG by six different algorithms, and the mean of the six measurements was analyzed. In each recording of each individual, QT-RR relationship was assessed by 10 different regression models including linear ($QT = \beta + \alpha \times RR$) and parabolic ($QT = \beta \times RR^\alpha$) models. Standard deviations (SDs) of regression parameters α and β of consecutive recordings of each individual were compared with SD of the individual means. Intrasubject stability and interindividual variability were further tested by ANOVA. With all models, intraindividual SDs of the regression parameters were highly significantly smaller than SD of individual means ($P < 10^{-5}$ – 10^{-9}). The intrasubject stability was further confirmed by ANOVA ($P < 10^{-19}$ – 10^{-30}). The QT-RR relationship exhibits substantial intersubject variability as well as a high intrasubject stability. This has practical implications for a precise estimation of the heart rate-corrected QT interval in which optimized subject-specific rate correction formulas should be used.

corrected QT interval; repolarization

THE RELATIONSHIP between duration of the QT interval and heart rate has long been debated. Studies of this relationship are particularly important for improved calculations of heart rate-corrected QT interval, which is a recognized marker of arrhythmic risk (7, 26, 33, 34) including the risk of drug-induced proarrhythmia (12). Although many mathematical models have been proposed to describe the QT-RR relation, none of the

models (and corresponding heart rate correction formulas) has been accepted as universally applicable (1, 10, 13, 19, 29). As repeatedly pointed out, any formula describing the relationship between the QT interval and the preceding RR interval is limited by physiological factors, such as the extra-heart rate influences on myocardial repolarization (4, 5, 30) and the “lag hysteresis” of the QT-RR relationship (8, 17).

Less attention has so far been paid to individual differences in the QT-RR relationship, which also limit the success of any “universal” mathematical model and contribute to the errors of any fixed heart rate correction formula. Substantial interindividual differences of the QT-RR relationship have been reported (6, 25) but, until recently, not studied systematically.

In a recent study (22), the 24-h QT-R relationship of 50 healthy subjects was investigated with different generic regression models. With all these models, the regression parameters varied very significantly between different individuals. For example, with the parabolic model ($QT = \beta \times RR^\alpha$), the individually optimized coefficient α varied from 0.23 to 0.49, that is, the interindividual differences were greater than the difference between the Bazett ($\alpha = 0.5$) and Fridericia ($\alpha = 0.33$) corrections.

These results strongly suggest that the traditional approach for rate correction of the QT interval with the Bazett correction or any other fixed formula is at best problematic. A formula that appropriately corrects the QT intervals (i.e., renders them heart rate independent) in one individual may significantly over- or undercorrect in another individual.

There are several possible reasons for the high interindividual variability. These include environmental influences and interindividual differences in heart rate variability as well as inherent genetically determined differences in the QT-RR pattern. To differentiate between these possibilities, the intraindividual stability and the interindividual variability must be compared.

With this in mind, this study was designed to investigate systematically the intraindividual and interindividual variations of the QT-RR relationship. For this

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purpose, a series of repeated 24-h 12-lead electrocardiographic (ECG) Holter recordings was obtained in a group of healthy subjects.

METHODS

Study population. The study investigated 75 subjects (42 women, mean age 27.9 ± 9.6 yr, range 18–59 yr; 33 men, mean age 26.8 ± 7.5 yr, range 18–43 yr) with no history of cardiac disease, a normal physical examination, and a normal baseline 12-lead ECG. No drugs were taken by any participant for at least 2 wk before the first recording and/or during the subsequent phases of the study. The study was approved by the local ethics committee, and all participants gave written consent.

Data acquisition. In each subject, four consecutive 24-h 12-lead ECG Holter recordings (250 Hz, 12-bit analog-to-digital resolution; SEER MC digital recorder; GE Marquette, Milwaukee, WI) were obtained. After a baseline recording, subsequent recordings were obtained after 24 h, 1 wk, and 1 mo. The participants were either employees of St. George's Hospital and the Medical School or undergraduate medical students. The recordings were obtained during standard working days, and although the participants were asked to refrain from substantial physical excesses of their usual daily routine, no other attempts were made to standardize environmental influences during the recording phases. Generally, the environment and occupational routines under which the recordings were obtained were fairly similar for all participants.

One 10-s ECG was recorded every 30 s for the whole nominal 24-h Holter recording. To avoid confusion, we use the term "ECG recording" to describe the 24-h 12-lead ECG Holter recording and the term "ECG sample" to describe the individual 10-s 12-lead ECG snapshot.

QT interval measurement. It was technically impossible to measure the QT interval in all ECG samples manually, because the study involved ~840,000 individual ECG samples. Therefore, all ECG samples were processed automatically with the following strategy developed to improve the accuracy of algorithmic QT interval measurement. A lead-specific median ECG beat was constructed from the sinus beats in each 10-s ECG (37). The QT interval was measured in each lead of each median ECG beat by six different automatic methods of the QT Guard package (GE Marquette; Ref. 37). For *methods 1* and *2*, the intersect between the baseline and the downslope tangent of the T wave was computed from the interpolation of 6 (*method 1*) and 12 (*method 2*) samples around the inflex point. For *methods 3–6*, the final drop of the ECG signal (*methods 3* and *4*) and of its first derivative (*methods 5* and *6*) below 5% (*methods 3* and *5*) and 15% (*methods 4* and *6*) of the maximum value within the T wave were used.

For each of these methods, the median QT interval among all measurable leads was obtained for each ECG sample. The QT measurement of an ECG sample was accepted if at least six leads were measurable (as judged by the QT Guard package; Ref. 37) and if the median QT intervals provided by the six methods differed by ≤ 40 ms. The threshold of six measurable leads and 40-ms difference between different methods was based on previous experience with the QT Guard package (2). If the measurement was accepted, the average of the six median QT intervals was taken as the valid QT interval.

Compared with the maximum QT interval of all measurable leads, the automatically measured median QT interval provides superior data stability (21). In healthy hearts, one is

also unlikely to observe substantial T wave abnormalities in only one lead ("regional" QT prolongation; Ref. 21), and hence, the difference between median and maximum QT interval is less expressed than in patients with repolarization abnormalities and/or nonspecific T wave changes.

Heart rate measurement. Within each ECG sample, individual cardiac cycles were identified by pattern matching between the median beat and the native ECG signal (23). From these, the average RR interval was obtained for each ECG sample.

To avoid mismatch between QT and RR intervals due to the hysteresis of QT-RR adaptation, only ECG samples with relatively stable heart rate were considered. For this purpose, linear regressions were calculated between the duration and the order number of individual RR intervals. ECG samples were excluded if, through the whole 10-s recording, RR intervals were significantly (judged by 95% confidence interval) rising or falling by ≥ 5 ms/interval. Although this permitted sinus arrhythmia in accepted ECG samples, the samples from episodes of systematic heart rate acceleration or deceleration were excluded.

Data analysis. Only ECG samples with accepted QT interval measurements and accepted stable RR interval measurements were considered. ECG recordings with at least 900 acceptable samples were used in the analysis. The limit of 900 samples was chosen arbitrarily to exclude ECG recordings with a poor definition of the QT-RR pattern. Finally, only data of subjects for whom all four repeated ECG recordings were acceptable were considered.

The QT-RR data of each 24-h recording were investigated with 10 different regression models. These models included a variety of mathematically defined functions the graphs of which resembled the possible physiological shapes of the QT-RR relationship. Thus the set of all the models was constructed to cover the physiological patterns as comprehensively as possible. By investigating all different models, the bias was avoided that might have otherwise been introduced by making inappropriate assumptions about the QT-RR relationship. The following regression models were used: linear model ($QT = \beta + \alpha \times RR$); hyperbolic model ($QT = \beta + \alpha/RR$); parabolic log/log model ($QT = \beta \times RR^\alpha$); logarithmic model [$QT = \beta + \alpha \times \ln(RR)$]; shifted logarithmic model [$QT = \ln(\beta + \alpha \times RR)$]; exponential model ($QT = \beta + \alpha \times e^{-RR}$); arcus tangent model [$QT = \beta + \alpha \times \arctan(RR)$]; hyperbolic tangent model [$QT = \beta + \alpha \times \tanh(RR)$]; arcus hyperbolic sine model [$QT = \beta + \alpha \times \operatorname{arcsinh}(RR)$]; and arcus hyperbolic cosine model [$QT = \beta + \alpha \times \operatorname{arccosh}(RR + 1)$].

In all formulas the QT and RR intervals were expressed in seconds. All models were designed to have two regression parameters to make the closeness of regression fit easily comparable.

Statistical analysis. With each regression model, four values of the parameters α and β were obtained from the repeated ECG recordings of each subject with custom-written software. These were averaged for each individual, and the individually mean parameters in men and women were compared with a nonparametric two-sample Wilcoxon test.

To compare the intra- and intersubject differences of the regression parameters, the standard deviations of α and β in each participant were compared with the standard deviation of the subject-specific mean values of α and β with a nonparametric one-sample Wilcoxon test. To eliminate the influence of sex differences on the intersubject variability, the comparison of intra- and intersubject standard deviations was repeated separately for the groups of men and women in the study. The intrasubject reproducibility of individual re-

gression parameters from the repeated recordings was also compared with repeated-measures ANOVA.

To compare the closeness of fit of the different regression models, the averaged residuum was obtained for each ECG recording and each model. For each subject, the regression model was identified that led to the lowest residua averaged over the four ECG recordings. The residua of different models were compared with a nonparametric one-sample Wilcoxon test. Statistica version 5.1 (StatSoft) was used for analysis.

Data are presented as means \pm SD unless otherwise stated. A P value <0.05 was considered statistically significant.

RESULTS

Figure 1 shows examples of QT-RR patterns of the repeated recordings in two women and two men. The patterns clearly suggest both substantial intersubject variability and high intrasubject stability of the QT-RR relationship. Figure 1 also confirms that in addition to heart rate, there are other important determinants of QT interval, because at the same RR interval, QT interval differed substantially in different ECG samples.

Of all subjects, 46 had all four ECG recordings accepted for analysis (22 men and 24 women, 26.8 ± 7.3

and 27.3 ± 8.1 yr, respectively; $P =$ not significant). The 184 accepted ECG recordings contained on average $1,504 \pm 283$ ECG samples/recording. The intervals between the first and subsequent ECG recordings were 1.0 ± 0.0 , 7.7 ± 2.0 , and 31.2 ± 3.9 days, respectively.

Table 1 shows the regression parameters α and β for all regression models in men and women. Except for the α parameter of the hyperbolic model, the regression parameters of all models differed significantly between the sexes. In general, women had steeper and more curved QT-RR patterns than men.

Table 2 shows the distribution of the optimum regression models as judged by the regression residua. In 52% of all subjects the linear or the arcus hyperbolic sine model led to the best fit to the QT-RR data, whereas the parabolic model was optimal in only 4% of the subjects and the hyperbolic model in none.

The intrasubject and intersubject variability of the regression parameters in all subjects, in women, and in men are compared in Table 3. With all models, the within-individual standard deviations of both parameters were highly significantly smaller than the standard deviations of individual means. The ANOVA analysis confirmed a highly significant intrasubject

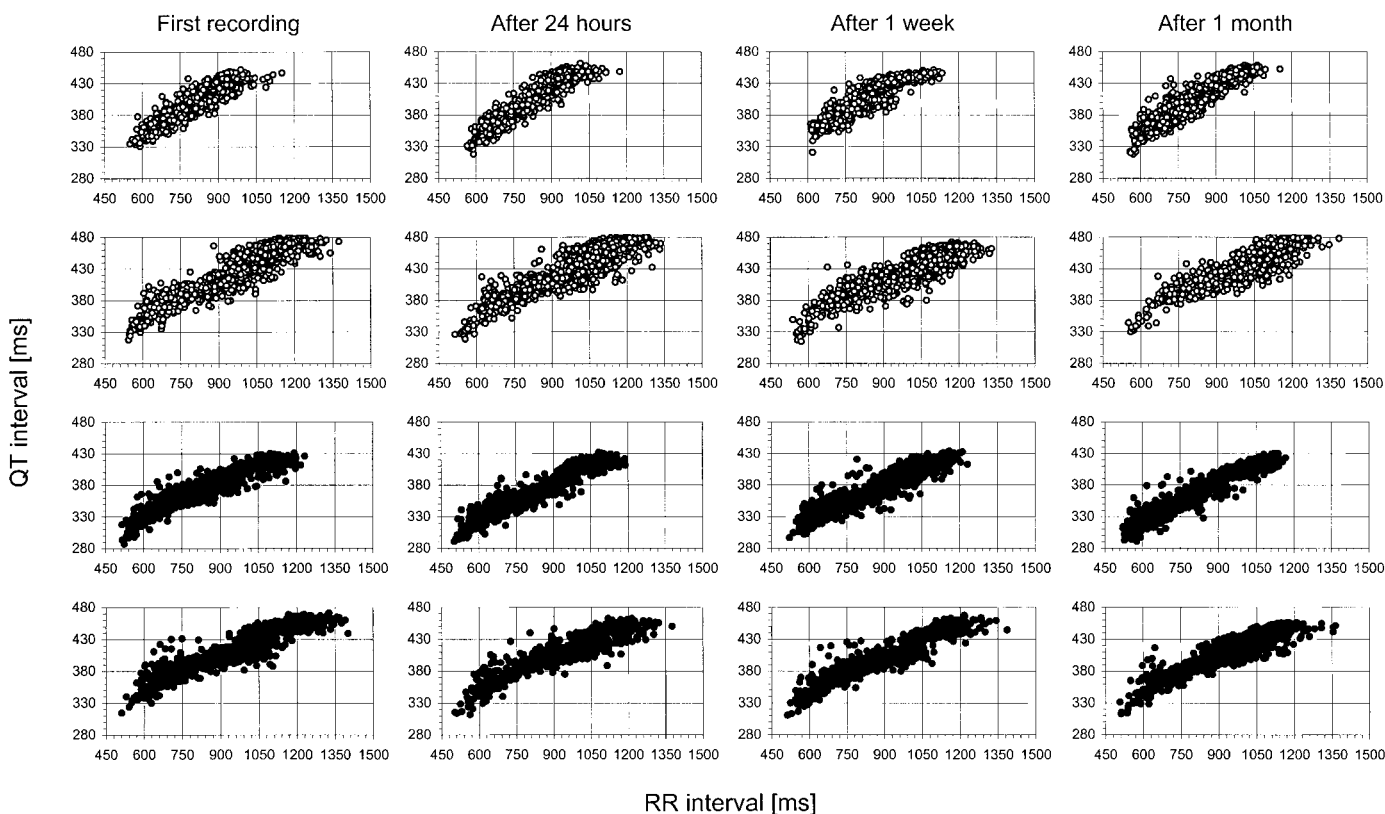


Fig. 1. Examples of QT-RR patterns of the repeated recordings in 2 women (top 2 rows; \circ) and 2 men (bottom 2 rows; \bullet). Each row presents 4 recordings of 1 subject, and the 4 columns present the 1st and subsequent recordings of all subjects, respectively. Note the stability of the QT-RR pattern in each subject and the variability of the patterns in different subjects. Note also that at the same RR interval, the QT interval differed substantially in different electrocardiographic samples. However, in this aspect, the figure is potentially misleading because it shows only the range of all QT intervals measured at the same heart rate rather than their distribution. A detailed analysis (not presented in this article) showed that on average, the 90th percentile spread of QT intervals recorded at the same heart rate varied <20 ms in both women and men.

Table 1. Individual values of regression parameters α and β in men and women

Model	Parameter α			Parameter β		
	Men	Women	P value	Men	Women	P value
Linear	0.163 ± 0.018	0.203 ± 0.031	3.3×10^{-5}	0.242 ± 0.016	0.225 ± 0.023	4.3×10^{-3}
Hyperbolic	-0.120 ± 0.018	-0.132 ± 0.022	0.060	0.527 ± 0.028	0.554 ± 0.035	4.7×10^{-3}
Parabolic (log/log)	0.370 ± 0.031	0.424 ± 0.043	3.7×10^{-5}	0.405 ± 0.012	0.427 ± 0.014	2.5×10^{-6}
Logarithmic	0.143 ± 0.014	0.165 ± 0.018	5.8×10^{-5}	0.406 ± 0.012	0.425 ± 0.014	1.1×10^{-5}
Shifted logarithmic	0.240 ± 0.026	0.300 ± 0.043	5.0×10^{-6}	1.259 ± 0.021	1.234 ± 0.031	2.7×10^{-3}
Exponential	-0.399 ± 0.039	-0.465 ± 0.050	2.3×10^{-5}	0.553 ± 0.024	0.597 ± 0.031	4.4×10^{-6}
Arcus tangent	0.294 ± 0.029	0.344 ± 0.037	1.6×10^{-5}	0.175 ± 0.017	0.156 ± 0.021	7.8×10^{-4}
Hyperbolic tangent	0.334 ± 0.038	0.381 ± 0.044	4.1×10^{-4}	0.152 ± 0.022	0.135 ± 0.024	0.019
Arcus hyperbolic sine	0.220 ± 0.021	0.265 ± 0.032	4.4×10^{-6}	0.212 ± 0.015	0.194 ± 0.020	2.0×10^{-3}
Arcus hyperbolic cosine	0.261 ± 0.024	0.308 ± 0.034	6.5×10^{-6}	0.062 ± 0.026	0.020 ± 0.036	4.6×10^{-5}

A values are means \pm SD of regression parameters α and β compared between men and women (2-sample Wilcoxon test) for 10 regression models.

repeatability of regression parameters compared with intersubject variability.

Figure 2 presents the distribution of individual values of the regression parameters for the linear model and arcus hyperbolic sine model, that is, the most frequent optimum models. It is clearly visible that the spread of the individual means of the regression parameters was substantially larger than the intrasubject variability.

Table 4 shows the comparison of the intrasubject stability of the regression parameters (expressed by standard deviations of the regression parameters derived from the 4 repeated ECG recordings in each subject) between women and men. With several regression models (including the linear and arcus hyperbolic sine model), the intrasubject stability was significantly or nearly significantly greater in men than in women. However (see Table 3), the differences in the individual stability between sexes were minute compared with the intersubject variability in the whole group.

DISCUSSION

Findings of study. With the use of a different population and more detailed analysis, this study confirms the previous findings (22) that the QT-RR relationship differs substantially between different healthy individuals. At the same time, the study also shows that the individual QT-RR pattern assessed from 24-h 12-lead

Holter recordings is stable over a period of (at least) 1 mo. The observation that the intraindividual variability is lower than the interindividual variability is not in principle surprising. However, it is the degree of the difference that is unexpected. Despite the broad similarity in the recording conditions, there were very substantial differences between different individuals. However, despite this large variability within the group, the individual patterns were surprisingly stable. Thus the results suggest that the inherent, probably genetically determined, differences in cardiac repolarization are substantially greater than the differences due to environmental influences and autonomic regulation. On the basis of these observations, it does not seem unreasonable to speculate that the individual QT-RR relationship has, in addition to autonomic and environmental influences, unique "fingerprint-like" properties.

Relation to previous studies. Although the sex differences in the QT-RR relationship pattern were already noted by Bazett (3), the individual variations of the QT-RR pattern have attracted much less attention. Because the QT-RR relationship in the general population is likely to vary within certain limits, it is possible that analyses of pooled data from very large populations can produce very similar values of interpopulation parameters purely due to regression to the mean [e.g., the Framingham (32) and Rotterdam (7) studies]. However, smaller studies, such as those from which most heart rate correction formulas have been derived, have very often produced substantially different values of parameters in proposed formulas for heart rate correction of the QT interval (see discussion in Ref. 22). Traditionally, these differences have been attributed to differences in heart rate, age, physiological conditions, etc., but not to inherently different individual QT-RR patterns.

The interindividual differences of the QT-RR regression parameters observed in this study are comparable to those previously reported between different clinically defined groups. For example, the slope of the linear QT-RR model in this study ranged from 0.137 to 0.199 in men and from 0.145 to 0.243 in women. These ranges are practically the same as the statistically

Table 2. Distribution of optimum regression models

Model	Optimum Cases		
	Men	Women	All
Linear	6	5	11
Hyperbolic	0	0	0
Parabolic (log/log)	1	1	2
Logarithmic	0	1	1
Shifted logarithmic	5	3	8
Exponential	1	1	2
Arcus tangent	0	2	2
Hyperbolic tangent	1	6	7
Arcus hyperbolic sine	8	5	13
Arcus hyperbolic cosine	0	0	0

Distribution of the optimum regression models in men, in women, and in all subjects. See text for details.

Table 3. Comparison of intrasubject and intersubject variability of regression parameters

Model	All subjects				Women				Men			
	Individual SD	Pool SD	Wilcoxon P value	ANOVA P value	Individual SD	Pool SD	Wilcoxon P value	ANOVA P value	Individual SD	Pool SD	Wilcoxon P value	ANOVA P value
<i>Parameter α</i>												
Linear	0.011 \pm 0.005	0.032	3.6 $\times 10^{-9}$	0	0.013 \pm 0.005	0.031	1.8 $\times 10^{-5}$	0	0.008 \pm 0.004	0.018	4.6 $\times 10^{-5}$	7.7 $\times 10^{-25}$
Hyperbolic	0.008 \pm 0.004	0.021	3.8 $\times 10^{-9}$	0	0.008 \pm 0.004	0.022	1.8 $\times 10^{-5}$	0	0.007 \pm 0.004	0.018	5.3 $\times 10^{-5}$	7.2 $\times 10^{-28}$
Parabolic	0.020 \pm 0.010	0.046	3.6 $\times 10^{-9}$	0	0.022 \pm 0.010	0.043	2.4 $\times 10^{-5}$	4.6 $\times 10^{-25}$	0.017 \pm 0.009	0.031	9.2 $\times 10^{-5}$	3.5 $\times 10^{-21}$
Logarithmic	0.008 \pm 0.004	0.019	4.1 $\times 10^{-9}$	0	0.009 \pm 0.005	0.018	2.7 $\times 10^{-5}$	1.6 $\times 10^{-26}$	0.007 \pm 0.004	0.014	5.3 $\times 10^{-5}$	1.4 $\times 10^{-23}$
Shifted logarithmic	0.016 \pm 0.008	0.046	3.6 $\times 10^{-9}$	0	0.019 \pm 0.008	0.043	1.8 $\times 10^{-5}$	0	0.012 \pm 0.006	0.026	4.6 $\times 10^{-5}$	7.0 $\times 10^{-25}$
Exponential	0.022 \pm 0.012	0.055	3.8 $\times 10^{-9}$	0	0.025 \pm 0.013	0.050	2.7 $\times 10^{-5}$	2.1 $\times 10^{-25}$	0.019 \pm 0.010	0.039	4.0 $\times 10^{-5}$	9.1 $\times 10^{-24}$
Arcus tangent	0.017 \pm 0.009	0.041	3.8 $\times 10^{-9}$	0	0.019 \pm 0.010	0.037	2.7 $\times 10^{-5}$	2.8 $\times 10^{-25}$	0.014 \pm 0.008	0.029	4.0 $\times 10^{-5}$	9.9 $\times 10^{-24}$
Hyp. tangent	0.019 \pm 0.011	0.046	3.8 $\times 10^{-9}$	0	0.022 \pm 0.011	0.044	2.7 $\times 10^{-5}$	1.1 $\times 10^{-26}$	0.017 \pm 0.010	0.038	4.6 $\times 10^{-5}$	5.4 $\times 10^{-26}$
Arcus hyp. sine	0.013 \pm 0.007	0.035	3.6 $\times 10^{-9}$	0	0.015 \pm 0.007	0.032	1.8 $\times 10^{-5}$	5.0 $\times 10^{-28}$	0.011 \pm 0.005	0.021	6.1 $\times 10^{-5}$	1.8 $\times 10^{-23}$
Arcus hyp. cosine	0.015 \pm 0.008	0.038	3.6 $\times 10^{-9}$	0	0.017 \pm 0.008	0.034	2.7 $\times 10^{-5}$	2.9 $\times 10^{-26}$	0.012 \pm 0.006	0.024	6.1 $\times 10^{-5}$	3.4 $\times 10^{-23}$
<i>Parameter β</i>												
Linear	0.008 \pm 0.004	0.022	3.6 $\times 10^{-9}$	0	0.009 \pm 0.004	0.023	1.8 $\times 10^{-5}$	0	0.007 \pm 0.004	0.016	4.0 $\times 10^{-5}$	6.5 $\times 10^{-28}$
Hyperbolic	0.011 \pm 0.006	0.034	3.6 $\times 10^{-9}$	0	0.011 \pm 0.006	0.035	1.8 $\times 10^{-5}$	0	0.010 \pm 0.006	0.028	4.6 $\times 10^{-5}$	0
Parabolic	0.003 \pm 0.002	0.017	3.6 $\times 10^{-9}$	0	0.004 \pm 0.002	0.014	1.8 $\times 10^{-5}$	0	0.003 \pm 0.001	0.012	4.0 $\times 10^{-5}$	0
Logarithmic	0.003 \pm 0.002	0.016	3.6 $\times 10^{-9}$	0	0.004 \pm 0.002	0.014	1.8 $\times 10^{-5}$	0	0.003 \pm 0.001	0.012	4.0 $\times 10^{-5}$	0
Shifted logarithmic	0.012 \pm 0.006	0.029	3.6 $\times 10^{-9}$	0	0.014 \pm 0.006	0.031	1.8 $\times 10^{-5}$	3.5 $\times 10^{-30}$	0.010 \pm 0.006	0.021	4.6 $\times 10^{-5}$	5.5 $\times 10^{-25}$
Exponential	0.011 \pm 0.006	0.035	3.6 $\times 10^{-9}$	0	0.013 \pm 0.006	0.031	1.8 $\times 10^{-5}$	0	0.009 \pm 0.005	0.024	4.0 $\times 10^{-5}$	0
Arcus tangent	0.011 \pm 0.006	0.021	1.1 $\times 10^{-8}$	0	0.012 \pm 0.006	0.021	9.1 $\times 10^{-5}$	5.7 $\times 10^{-21}$	0.010 \pm 0.006	0.017	2.6 $\times 10^{-4}$	1.6 $\times 10^{-18}$
Hyp. tangent	0.013 \pm 0.007	0.024	1.0 $\times 10^{-8}$	0	0.014 \pm 0.007	0.024	7.2 $\times 10^{-5}$	3.3 $\times 10^{-22}$	0.011 \pm 0.007	0.022	1.4 $\times 10^{-4}$	6.4 $\times 10^{-21}$
Arcus hyp. sine	0.009 \pm 0.005	0.020	4.1 $\times 10^{-9}$	0	0.010 \pm 0.005	0.020	2.4 $\times 10^{-5}$	1.1 $\times 10^{-25}$	0.008 \pm 0.004	0.015	1.2 $\times 10^{-4}$	2.7 $\times 10^{-21}$
Arcus hyp. cosine	0.017 \pm 0.009	0.038	4.3 $\times 10^{-9}$	0	0.020 \pm 0.009	0.036	3.0 $\times 10^{-5}$	2.2 $\times 10^{-23}$	0.015 \pm 0.008	0.026	1.4 $\times 10^{-4}$	1.0 $\times 10^{-19}$

For each of the 10 regression models, the mean of the individual standard deviations (SD) of the regression parameters α and β (i.e., standard deviation of the 4 recordings in each subject; Individual SD) was compared with the SD of the individual means (Pool SD; shown in Table 1). The comparisons were performed with 1-sample Wilcoxon test. ANOVA tests were used to compare intrasubject stability and intersubject variability of individual regression parameters. Hyp, hyperbolic.

significant differences reported between groups of patients with exercise-induced ventricular tachycardia with and without structural heart disease (11) or between patients with idiopathic ventricular fibrillation and healthy subjects (36).

With multiple QT-RR data from standard Holter recordings in 21 healthy subjects, Molnar et al. (25) compared five correction formulas with individually optimized formulas derived from the data of each patient. They found that the individual optimizations were superior to conventional heart rate corrections.

Davey (6) estimated the slope of the individual QT-heart rate linear regression lines during exercise in healthy subjects and patients with hypertrophic cardiomyopathy and heart failure. He obtained corrected QT intervals (QTc) by extrapolating the QT-heart rate regression line to a heart rate of 60 beats/min in each participant. These "individual" QTc separated the three study groups better than the Bazett-corrected QTc and, unlike the latter, were not correlated to the heart rate. No previous author, to our knowledge, has investigated or even formulated the problem of the stability of the individual QT-RR pattern.

Lecocq et al. (18) studied the QT-RR relationship of 11 subjects at rest, during exercise, and after intravenous isoproterenol and of 12 subjects at rest and after oral propranolol. An exponential model ($QT = A - Be^{-k \times RR}$, where A , B and k are the regression parameters) was fitted to the QT-RR data. Four subjects participated in both studies conducted 10 mo apart. When comparing individually the equations from both studies, the authors mentioned that they "... could not find any significant change between the 2 periods ..."

which was not commented on further but is in full agreement with the results of the present study.

Very recently, Malik (19) tested the practical appropriateness of an "individualized" rate correction approach in a study of drug-induced QT interval prolongation. That study suggested that the individual QT-RR relationship could be reliably estimated from a much smaller number of QT-RR data pairs.

Not only the regression parameters but also the general form of the regression model that best fits the QT-RR data varied significantly among different individuals. The linear model ($QT = \beta + \alpha \times RR$; Refs. 7, 13, 32) was optimum in 31 out of a total of 96 participants in this study and in the previous study (22). On the other hand, the parabolic model ($QT = \beta + RR^2$), from which the Bazett formula (3) and other popular heart rate correction formulas (9, 14) have been derived, was optimum in only seven subjects, whereas the hyperbolic model ($QT = \beta + \alpha/RR$; 15) was not an optimum in any subject. Different models reported in the literature have been tested in very different databases [pooled data of all subjects, multiple recordings in each subject, or even a mixture of both, as in the original study of Bazett (3)] under different physiological conditions (rest, exercise test, or 24-h recordings), various heart rate ranges, and numbers of QT-RR samples. To our knowledge, no previous study has addressed systematically the distribution of different QT-RR regression shapes in a healthy population.

These results [as well as those of our previous study (22)] should not be interpreted as a suggestion of the superiority of any regression model for studies of QT-RR relationship in the general population. On the

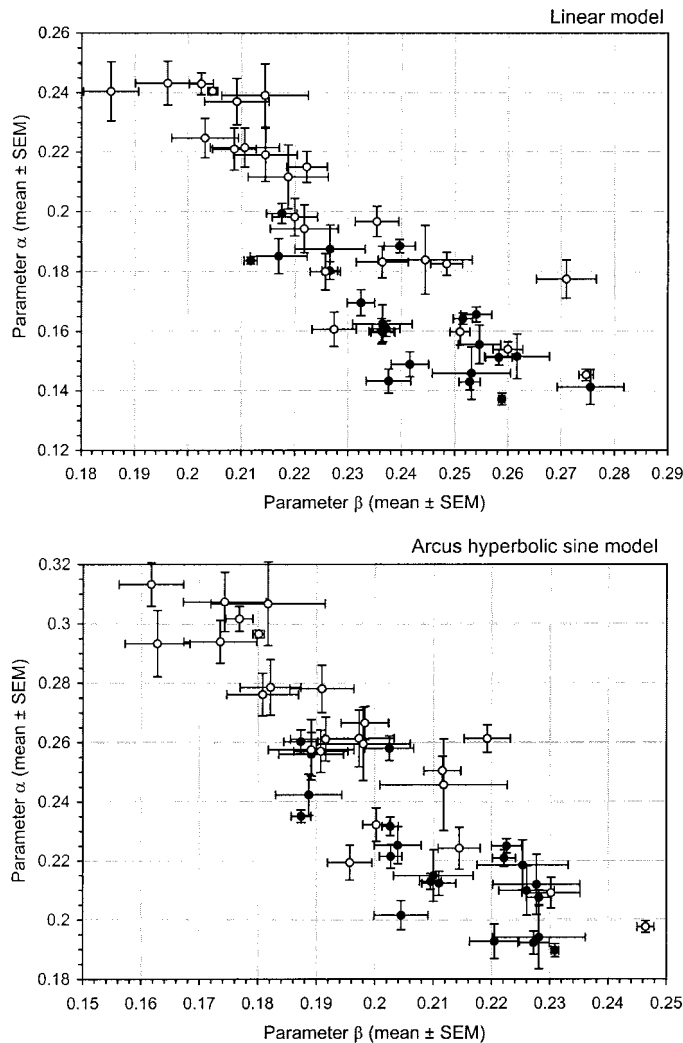


Fig. 2. Intrasubject and intersubject variability of the regression parameters of men (\bullet) and women (\circ) with the linear model (top) and the arcus hyperbolic sine model (bottom). Error bars represent the SE of the mean of the 4 recordings repeated in each subject (the corresponding SDs are twice as large). See text for details.

contrary, it seems that no “superior” or “physiological” QT-RR regression model exists. It is likely that similar intersubject difference and intrasubject stability also exist in the shapes of QT-RR relationships and that different individuals would be best studied with different regression curvatures. Analyses of different groups of healthy subjects and/or cardiac patients would most likely render significantly different (and probably non-reproducible) distributions of the “optimum” regression models.

It can be speculated that the intersubject variability of the QT-RR pattern may reflect interindividual variations in the expression and/or autonomic control of different ionic repolarizing currents. It is known that different gene mutations affecting different repolarizing currents lead not only to different TU morphologies but also to distinctly different patterns of adaptation of QT interval duration to exercise and other autonomic stimuli (27, 35). Furthermore, it has been demon-

strated that even phenotypically normal long-QT syndrome gene carriers may exhibit characteristic changes in QT dynamicity (16). Recent studies have suggested that the frequency of asymptomatic long-QT syndrome gene carriers in the general population is greater than previously considered (28). Whether “normal” genetic variations or various silent gene mutations are the cause of the diversity of QT-RR relationship patterns in the population is not known. If the latter is the case, it remains to be determined whether particular QT-RR patterns signify slight variations in “repolarization reserve” (28) and differences in the propensity to repolarization-related arrhythmias, such as those induced by repolarization active drugs. The genetic background of the stable QT-RR pattern is also more likely than other, e.g., environment-related determinants, because the participants of our study were recorded during normal daily routines with variable levels of mental and physical stress that are very unlikely to remain stable over a period of 1 mo.

The slightly lower intrasubject stability in women compared with men might have been contributed by menstrual cycle-related variability or by the positional variability of ambulatory precordial electrodes in women.

Limitations of study. Our study has several important technical and physiological limitations. The major technical limitation is the reliance on automatic measurement of QT intervals without the possibility of systematic visual verification and manual editing of many thousands of ECG samples. Not only the type of automatic measurement algorithm (24) but even differences in the parameter setting within one algorithm can significantly influence the measurement results (2). Although we used an advanced strategy for improving the quality of automatic QT measurement, the principal problem of automatic measurement remains. The exclusion of 10-s ECG samples with significant variations of the heart rate most likely has signifi-

Table 4. Comparison of intrasubject stability between women and men

Model	P Value	
	Parameter α	Parameter β
Linear	0.00770	0.06274
Hyperbolic	0.46499	0.53441
Parabolic (log/log)	0.08037	0.02768
Logarithmic	0.17093	0.03683
Shifted logarithmic	0.00884	0.05375
Exponential	0.15105	0.03108
Arcus tangent	0.13295	0.15748
Hyperbolic tangent	0.17797	0.22465
Arcus hyperbolic sine	0.01705	0.07656
Arcus hyperbolic cosine	0.05101	0.08037

P values (nonparametric U-test) of the comparison of individual SDs of the regression parameters α and β (i.e., SD of the parameters derived from the 4 recordings in each subject) between women and men. The compared values of women and men are shown in Table 3 as Individual SD [e.g., the individual standard deviations of parameter α of the linear model were 0.013 ± 0.005 in women and 0.008 ± 0.004 in men; $P = 0.00770$ (see Table 3)].

cantly diminished, but not completely removed, the effect of QT hysteresis, because the changes in QT interval duration after abrupt changes in heart rate are completed only in ~ 3 min (17). However, these potential technical inaccuracies could only have caused our assessment to underestimate the degree of intrasubject stability of QT-RR patterns.

Instead of the maximum QT interval among all measurable leads, we used the median QT interval duration. In healthy individuals, a range of QT intervals measured in different ECG leads has been repeatedly reported around only 20–30 ms and attributed predominantly to measurement inaccuracies and differences in T wave loop projection (20). Moreover, the maximum QT interval is more likely influenced by measurement inaccuracies that are bound to be present with fully automatic measurement. Thus with the automatic QT interval measurement, the median QT interval is both relevant and a more stable representation of repolarization duration in healthy subjects. However, to ensure that no bias had been introduced, we also recomputed the whole study with the maximum QT interval of all measured leads and with the limit of 60 ms as a permissible threshold for the discrepancy between the different measurement algorithms. Although the QT-RR regression residua increased (there were obvious artificial outliers in the QT interval data), the principal results of the study remained the same ($P < 10^{-4}$ – 10^{-9} for the comparison of individual SD vs. the SD of individual means of regression coefficients).

Although we observed that different QT-RR regression models optimally fit the data of different subjects, our statistical comparisons were based on fitting the data of all subjects with the same model. This is because the numerical differences between coefficients of different regression models are difficult to compare and the spread of the individual QT-RR patterns would be difficult to quantify if the different patterns were described with different models. This approach might have led to underestimation of the differences between intrasubject stability and intersubject variability because forcing individual QT-RR data into a nonoptimum regression equation may increase intrasubject variability. Instead of the battery of different biparametric regression models, it might have been more appropriate to develop a more flexible regression model with more parameters that would have described not only the slope and intercept but also the different properties of the optimum curvature fitting the QT-RR data. However, simple attempts of this kind (e.g., $QT = \chi + \beta \times RR^\alpha$, where χ is a regression parameter) are easily influenced by atypical outliers in the data and lead to physiologically unrealistic equations (e.g., $\alpha > 1$).

Our observations made in healthy young subjects may not necessarily be applicable to the general population and/or cardiac patients. It is not clear how much the individual QT-RR relationship might be influenced by pathological (e.g., subclinical evolution of the underlying heart disease) or pharmacological factors.

Finally, the protocol of our study did not include the investigation of cellular electrophysiological mechanisms and/or collection of genetic material that would permit us to link the differences in QT-RR patterns to the subclinical differences in cellular electrophysiology and/or in genes responsible for different repolarization channels. We also have not collected data on the menstrual cycle in women and are therefore unable to comment on the influence of menstrual cycle on the (small) intrasubject variability of QT-RR patterns.

Implications of study. These results provide the physiological basis for a new approach for heart rate correction of the QT interval based on estimation of the individual QT-RR pattern. In studies requiring an increased precision, current strategies for rate correction of the QT interval should be reevaluated. The use of a fixed rate correction formula should probably be restricted only to cases when approximate estimation of the corrected QT interval is sufficient and within a narrow band of physiological heart rates. In investigations requiring precise heart rate correction of the QT interval, e.g., in studies assessing the effect of drugs on QT interval duration, the use of an individual rate correction formula derived in each patient from multiple QT-RR data in a baseline, drug-free state should be adopted as a standard approach. To derive this formula, the optimum QT-RR regression model should first be identified in each individual. If the design of the study permits, the investigation of QT interval changes (e.g., drug related) should include not only the assessment of the changes of heart rate-corrected QT interval but also the changes of QT-RR pattern.

The present study as well as our previous study (22) clearly showed that any standard “ad hoc” accepted rate correction formula can lead to substantial under- or overcorrection of the QT interval in a large number of individuals, even with relatively small changes of the heart rate (e.g., 70–90 beats/min).

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